REMARKS

Claims 84, 89-93, 95, 97-104, 109 and 114 are pending following entry of the amendment above. Claims 84, 95, 103 and 104 have been amended to recite an alphavirus "replicon" particle. Accordingly, Claims 85, 96, 105-108, and 110-113 have been cancelled without prejudice. Claims 109 and 114 have been amended to depend from Claims 84 and 95, respectively, rather than canceled Claims 105 and 110. Claims 91, 92, 100 and 101 have been amended to recite a "naturally occurring cancer cell antigen" to provide better antecedent basis. These amendments have been made to put the application in better condition for allowance, and Applicants respectfully request entry thereof.

Applicants note with appreciation that many of the previous rejections and objections have been withdrawn. The remaining issues under 35 U.S.C. §102 and §103 are addressed below.

I. **Interview Summary.**

Applicants wish to express their appreciation for the time and courtesy extended by the Examiner toward Applicants' representative, Karen Magri, during the telephonic interview of 29 October 2003 in connection with this application. During the interview, the §103 rejections were discussed. Further, it was proposed that Applicants submit an additional Declaration under 37 C.F.R. § 1.132.

II. **The Finality of the Office Action is Premature.**

As discussed during the telephonic interview, Applicants submit that the finality of the present Office Action is improper, and request that, if a Notice of Allowance is not issued following consideration of this Amendment, the Examiner withdraw the finality of the rejection. The Action states, at page 10, point 15, that "Applicant's amendment necessitated the new ground(s) of rejection presented in this Office Action. Accordingly, this action is made

final." Applicants respectfully disagree as at least two of the new grounds of rejection were not necessitated by Applicants' previous amendment.

The M.P.E.P. § 706.07(a) states that:

> Under present practice, second or any subsequent actions on the merits shall be final, except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p).

In the instant case, at page 7 (lines 1-5), with respect to the rejections under §103 over Dubensky, the Johnston references and Falo, the Office Action states: "However it is noted that the Examiner erred in his statement of the teachings of Dubensky in the prior action. As indicated above, and in the prior action in the 102 rejection over Dubensky, the reference teaches the use of cancer cell antigens that appear to fall within the scope of the presently rejected claims." Thus, the Examiner has provided a new basis for these §103 rejections, which Applicants have not previously had an opportunity to address on the record, and which were not necessitated by Applicants' previous amendments.

Further, in the paragraph spanning pages 11-12, the Office Action states that: "The Applicant has amended the claims such that they now read on the use of naturally occurring cancer antigens as defined by the applicant in the Supplemental Response filed on April 25, 2003. . . . The amendment, which serves to clarify what was meant by a 'native cancer cell antigen', also distinguishes between the antigens taught by Falo, and the ones used in the present application." Applicants agree that this amendment was merely clarifying in effect and did not change the scope of the claims, and was submitted following the previous telephonic interview during which the Examiner indicated that this language was preferable to the language "native

cancer antigen." Thus, this amendment did not change the scope of the claimed invention and did not necessitate the new basis for the §103 rejection over Dubensky (discussed in the previous paragraph).

Likewise, the new rejection under §103 over U.S. 6,468,982 (Weiner et al.) was not necessitated by Applicants' previous amendments. At page 8, point 12, the Office Action states that: "The rejected claims have been described above. They have been amended such that they now read on naturally occurring cancer antigens that need not be native to the recipient host." Again, Applicants contend that the amendment to recite a "naturally-occurring cancer cell antigen" did not change the scope of the claims. Applicants have clearly indicated in their written responses and during the previous telephonic interview that a "native cancer antigen" can be any naturally occurring cancer antigen or an antigenically similar molecule and have never suggested that this term should be construed to mean that the antigen is derived from a particular patient (*see, e.g.*, Amendment of March 26, 2002, pages 4-5). Thus, Applicants' amendments in no way necessitated the new rejection over Weiner et al.

In view of the foregoing, Applicants submit that the finality of the present Office Action is premature. In the event that a Notice of Allowance is not issued after consideration of this response, it is requested that the finality of the present Office Action be withdrawn.

III. §102 Rejection over Dubensky.

In the outstanding Office Action, the §102(e) rejection over U.S. Patent No. 5,843,723 (Dubensky et al.) was withdrawn with respect to Claims 84, 85, 92, 93, 95, 96, 98, 100 and 102. However, this rejection was maintained with respect to Claims 105, 106, 109, 110, 111 and 114. Claims 105, 106, 110 and 111 have been cancelled. Claims 109 and 114 have been amended to depend from Claims 84 and 95, respectively. Accordingly, Applicants

respectfully submit that this rejection is now moot, and respectfully request withdrawal thereof.

IV. §103 Rejections over Dubensky or Johnston 1 in view of Falo and Johnston 2.

Claims 84, 85, 90-93 and 95-104 stand rejected under §103(a) as allegedly obvious over either Johnston I (WO 95/32733) or Dubensky in view of Johnston 2 (U.S. 5,792,462) and Falo et al. (U.S. 5,951,975). The Office Action states that Dubenksy teaches the use of cancer cell antigens that appear to fall within the scope of the presently rejected claims (citing Col. 19, lines 1-14 and Cols. 23-24). The Office Action further states that the reference does not teach the use of attenuated replicon particles; however, it is stated that the use of attenuated alphavirus particles for the use of inducing an immunogenic response against a heterologous antigenic protein is taught by Johnston 1 and Johnston 2. These rejections are respectfully traversed below.

As discussed at length during the telephonic interview, it is Applicants' position, that (1) there would have been no motivation to combine Dubenksy or Johnston 1 with Falo, (2) even if the references were combined, they would not have suggested the present invention, (3) the Dubensky reference is not enabling, (4) none of the references alone, or in any combination, would have provided the requisite expectation of success, and (5) the presently-claimed alphavirus replicon compositions have unexpectedly superior properties in treating cancer. Each of these points is addressed in turn below.

One of ordinary skill in the art at the time of invention would not have combined the teachings of Dubensky or Johnston 1 with Falo. As addressed in Applicants' previous arguments, the Falo et al. reference does not concern alphavirus-based vaccines or immunization with a naturally occurring cancer cell antigen (or antigenically similar molecule). As discussed in the **Declaration of Dr. Ian Caley under 37 C.F.R. § 1.132** (*hereinafter*, "the Caley Declaration; copy enclosed h rewith), the approach taken by Falo is

premised on the belief that direct immunization with a natural tumor antigen will not produce a sufficient anti-tumor immune response (Caley Declaration, para. 4). Thus, the tumor antigens are co-presented with an "artificial" antigen that elicits a strong immune response and a "cross-priming" response against the tumor antigens.

Further, as recognized by the Examiner and discussed by the Caley Declaration (para. 5), the presently claimed alphavirus compositions are readily distinguished from the artificial antigen vaccines taught by Falo et al. First, the claimed alphavirus compositions do not encode an "artificial" antigen. The claimed compositions are directed to alphavirus replicon particles encoding a naturally occurring cancer cell antigen or antigenically similar molecule. Second, the presently-claimed alphavirus compositions can be directly administered to a subject, without the necessity of *ex vivo* manipulation of tumor cells as required by Falo et al. (Caley Declaration, para. 5). Moreover, the Office Action acknowledges that the naturally occurring cancer antigens recited by the present claims are distinct from the artificial antigens of Falo et al. (Office Action, sentence spanning pages 6-7 and page 10, lines 1-2).

As noted by the Caley Declaration (para. 6), there are fundamental differences between the artificial antigen vaccines and methods of Falo et al. and the claimed alphavirus compositions and the uses and properties thereof. Thus, one of ordinary skill in the art would not have made the combination of Dubenksy or Johnston 1 with Falo et al. to arrive at the present rejection. The ordinarily skilled worker would have seen no relevance of the Falo et al. patent to the alphavirus work described by the Dubensky and Johnston 1 documents, and would not have modified the alphavirus compositions described in these primary references based on Falo et al.

Further, even if the cited references were combined, they would not have provided any motivation or suggestion for the presently-claimed alphavirus compositions encoding a naturally occurring cancer cell antigen. The artificial antigens of Falo et al. are readily distinguished from the native

cancer cell antigens that are encoded by the claimed alphavirus compositions. Indeed, Falo et al. teaches away from the presently claimed alphavirus vaccines as the strategy adopted by Falo et al. is premised on the assumption that direct immunization with a native cancer cell antigen will not be effective (Caley Declaration, para. 4). Thus, the combination of the artificial antigens of Falo et al. and the alphavirus vectored anti-pathogen vaccines of Johnston 1 or Dubensky would not provide motivation to make an alphavirus cancer vaccine expressing a naturally occurring cancer cell antigen.

Moreover, the Dubensky reference is not enabling for an alphavirus-based vaccine encoding a naturally-occurring cancer cell antigen. As pointed out in the Caley Declaration (para. 13), one skilled in the art would have been aware of the significant hurdles for an effective cancer vaccine. For example, it was known at the time of invention that cancer antigens are poorly immunogenic, host tolerance interferes with a robust immune response against naturally occurring cancer cell antigens, and that prior art cancer vaccine approaches were generally ineffective (Caley Declaration, para. 13). In addition, as discussed above and in the Caley Declaration (para. 7), Weiner et al. would further cast doubt on the suitability of an alphavirus vectored vaccine in view of the known disadvantages of viral vectors (*see, e.g.*, Weiner et al. at Col. 3, lines 30-50). Thus, one skilled in the art at the time of invention would have looked at the prophetic and speculative statements in Dubensky with considerable skepticism and would not have viewed the Dubensky reference as providing a credible and enabling disclosure of an alphavirus composition encoding a naturally occurring cancer cell antigen.

To support a *prima facie* case of obviousness, the references must provide motivation for one of ordinary skill in the art to practice the claimed invention as well as provide a reasonable expectation of success. As discussed at length during the telephonic interview, the cited references, alone or in combination, do not provide the requisite reasonable expectation of success. For the reasons discussed in the previous paragraph, one of ordinary skill in the art at the time of invention could not have had any

reasonable expectation in advance that an alphavirus composition expressing a naturally occurring cancer cell antigen could be used to elicit an anti-cancer response, and the prophetic statements of Dubensky would have at most been viewed as a proposal for future research, but would not have provided any reasonable expectation of success.

The present claims have been amended to recite alphavirus "replicon" particles. As outlined in the Caley Declaration (para. 9), replicon particles are capable of one round of infection; they cannot spread to (*i.e.*, infect) other cells. The cells that are infected by the replicon will eventually die due to cytopathogenic effects of the infection. During that limited timeframe, the replicon amplifies and expresses the naturally-occurring cancer cell antigen at a sufficiently high level to produce an effective anti-cancer response. There could not have been any reasonable expectation of success prior to the present invention that the alphavirus replicon particles would achieve this high level of expression and host immune response in this relatively short time period. While not wishing to be limited by any theory of the invention, it is believed that the superior results achieved with the claimed alphavirus replicon compositions are attributable to a combination of features, *e.g.*, the replicon specifically infects the antigen-presenting cells of the immune system, triggers both cellular and humoral immune responses, and expresses the cancer antigen at high levels (Caley Declaration para. 9).

During the telephonic interview, the Examiner suggested that Falo and Weiner (discussed in the next section) can be combined with the alphavirus work of Dubensky or Johnston 1 to provide the reasonable expectation of success with respect to the claimed alphaviral-based compositions. As discussed above, there would have been no motivation to combine the Falo and the Johnston 1 or Dubensky references. The approach taken by Falo to achieve an anti-cancer effect is so completely different from the claimed alphavirus compositions (Caley Declaration, paras. 6, 12 and 14), that one of ordinary skill in the art would not have viewed the results reported by Falo et al. as having any relevance to an alphavirus vectored system, nor would the

ordinarily skilled worker have extrapolated results described by Falo with an artificial antigen to the claimed alphavirus vaccine compositions (Caley Declaration, paras. 6, 12 and 14).

Even if, for the sake of argument, a *prima facie* case has been established, it is rebutted by the surprisingly superior properties and uses of the claimed alphavirus compositions. The unexpected and improved properties and uses of the claimed compositions have been discussed extensively in previous responses, which for the sake of conciseness will not be repeated here. To briefly summarize, the results provided in the two Olmsted Declarations and the Long abstract/poster demonstrate an important breakthrough in the field of cancer immunotherapy. The alphavirus vectored vaccine compositions of the invention are highly effective anti-cancer agents that avoid the need for artificial cancer cell antigens or *ex vivo* manipulation of cells.

Further, the presently claimed compositions have unexpected and superior properties in that they are effective to overcome tolerance and induce a protective immune response against a cancer antigen that would be recognized as self. The unexpected and superior properties of the claimed composition must be considered when assessing the nonobviousness thereof. *In re Papesch,* 137 USPQ 43 (CCPA 1963). *In re Papesch* has already been extensively discussed in Applicants' response of September 28, 2001, which discussion was sufficient to overcome the previous rejection over Johnston 1 in view of Falo et al.

Finally, to clarify the record, the Applicants wish to briefly address two points from the Office Action. The section of Dubenksy at Col. 19, lines 1-14, cited in the Office Action relates to a very different approach from the present invention. Discussion of this embodiment of the invention starts at Col. 18, line 18, of Dubensky and relates to methods of achieving tissue-specific expression of a nucleic acid. Thus, according to the Dubensky reference, this embodiment can be practiced to specifically express a cytotoxic protein in cancer cells, but not in healthy cells.

Further, at page 7 (lines 16-21), the Office Action states that:

> From the teachings of these references, it would have been apparent that the reason for deleting the genes encoding the structural genes from the replicon of Dubensky would be to achieve the same purpose as was achieved through the attenuating mutations of the Johnston references. It would therefore have been obvious to those of ordinary skill in the art to have used the attenuated vectors of the Johnston references in place of the inactivated vector of Dubenksy.

Applicants have previously pointed out that the modifications made to the alphavirus genome described by Dubenksy are not attenuating mutations and do not perform the same function as an attenuating mutation. It is Applicants' understanding from the telephonic interview that this point has been resolved; Applicants are providing these comments simply to clarify the record.

In summary, in view of the foregoing discussion, Applicants submit that the claimed alphavirus compositions are nonobvious over any combination of the cited references, and respectfully request withdrawal of the outstanding obviousness rejections.

V. §103 Rejection over Weiner et al. in view of Johnston 1 and Johnston 2.

The claims are newly rejected under 35 U.S.C. §103 as allegedly unpatentable over U.S. 6,468,982 (Weiner et al.) in view of the Johnston references. The Office Action states that Weiner et al. (Col. 14) teaches that genetic constructs that induce expression of the *neu* gene in cells can induce an immune response against hyperproliferative diseases including cancer. The Office Action further states that Weiner et al. does not teach the use of viral vectors to deliver these genetic constructs. The Office Action continues by stating that the Johnston references teach alphavirus vectors usable for the delivery of nucleic acids encoding antigenic peptides. The Office Action concludes that it would have been obvious to use the viral vectors of the Johnston references to deliver the nucleic acids as described by Weiner et al. The Office Action further notes (page 9, lines 4-6) that "the Weiner reference indicates that the described constructs represent an advance over the use of

viral vectors (Columns 3-4). However, this is not deemed to teach away from the use of other, older viral vectors." This rejection is traversed below.

Applicants' position with respect to Weiner et al. is similar to that presented above for the Falo et al. reference. There would have been no motivation to combine the Johnston references with Weiner et al., and even if the references were combined, the combination would not have suggested the present invention. Further, Weiner et al. does not provide a reasonable expectation of success in using alphavirus replicon vectors to treat cancer. Finally, the presently-claimed alphavirus vectors have unexpectedly superior properties in treating cancer that are not suggested by any of the references.

One of ordinary skill in the art at the time of invention would not have combined the Weiner patent with the Johnston references because these publications are directed to fundamentally different vaccine systems. As pointed out in the Caley Declaration (paras. 7-11), Weiner et al. uses "naked" nucleic acid constructs to administer a cancer antigen. This is a fundamentally different way of vaccine administration than a viral vectored vaccine (Caley Declaration, para. 11). Contrary to the assertion in the Office Action, an alphaviral vectored vaccine cannot deliver the nucleic acids of Weiner et al. By definition, the nucleic acid vaccines of Weiner et al. are not provided by any sort of vector. Nucleic acid vaccines are distinct from the claimed alphaviral-vectored vaccines and have a different mechanism of action therefrom (Caley Declaration, paras. 9-11). In view of these marked differences, one of ordinary skill in the art would not have made the combination of the Johnston references and the Weiner et al. patent.

Further, even if the combination were made, it would not have suggested the present invention to the worker of ordinary skill. The nucleic acid vaccines and genetic immunization approach of Weiner et al. are categorically different from the claimed alphavirus compositions and would not have provided any motivation or suggestion regarding an alphavirus vaccine encoding a naturally occurring cancer cell antigen (Caley Declaration, paras. 10 and 11). Indeed, Weiner et al. represents a distinct alternative to the

presently claimed alphavirus compositions, rather than a suggestion to use an alphaviral vectored vaccine (Caley Declaration, para. 7). In view of the pessimistic view of viral vaccines presented in Weiner et al., it cannot reasonably be said that this reference suggests or motivates the use of such vaccines. In fact, the only reasonable interpretation is that Weiner et al. teaches away from a viral vectored vaccine.

Further, Weiner et al. discusses the disadvantages of prior art viral vaccines, but is silent regarding alphavirus vaccines or, more specifically, alphavirus replicon particle vaccines. Moreover, contrary to the statements in the Office Action (page 9), Weiner et al. does not address the use of a viral vaccine to immunize against cancer. The cited portion of Weiner et al. (Columns 3-4) is addressing vaccines for immunizing against pathogens. The discussion of cancer vaccines at Col. 4, lines 18-38, makes no reference to viral vaccines at all. Thus, Weiner et al. does not disclose prior art viral vectored vaccines to treat cancer.

The combination of references cited in the present rejection would also have failed to provide a reasonable expectation of success to one of ordinary skill in the art with respect to the claimed invention. The Weiner et al. reference only teaches the disadvantages of viral vaccines and, as noted by the Examiner, the Johnston references are silent with respect to cancer antigens. As discussed above in connection with Falo et al., at the time of invention, the difficulties of vaccine approaches to treat cancer were known (see, Caley Declaration, para. 13). Further, the alphavirus replicon vaccines of the invention achieve a high level of amplification and expression of the cancer antigen within a limited timeframe and without spreading beyond the initial population of infected cells (Caley Declaration, para. 9). It would not have been obvious *a priori* that the alphavirus replicon vector would achieve sufficient expression and elicit an effective anti-cancer immune response in the host under these constraints. A reading of Weiner et al. would certainly have suggested that this approach would fail (Caley Declaration, para. 10).

During the telephonic interview, the Examiner suggested that the results disclosed by Weiner et al. for treating cancer would have provided a reasonable expectation of success in treating cancer using an alphavirus vaccine composition. One of ordinary skill in the art would not have combined these references or looked to Weiner et al. for guidance concerning an alphavirus vectored vaccine composition (Caley Declaration, paras. 11, 12 and 14). The genetic immunization and nucleic acid vaccines of Weiner et al. are so fundamentally different from alphavirus replicon vaccine compositions, such that the results disclosed by Weiner et al. with nucleic acid vaccines would not shed any light or provide any reasonable expectation of success with respect to the claimed alphavirus vaccines (Caley Declaration, para. 11, 12 and 14).

Finally, for the reasons discussed with respect to Falo et al., even if, for the sake of argument, the burden of making out a *prima facie* case has been met, the unexpectedly superior properties and uses of the claimed alphavirus compositions are sufficient to establish the non-obviousness of the claimed invention.

For the reasons presented above, Applicants submit that the claimed invention is unobvious over the combination of the Weiner et al. and the Johnston references, taken alone or in any combination. Accordingly, Applicants respectfully request withdrawal of the outstanding §103 rejection over these references.

VI. Conclusion.

The concerns of the Examiner having been addressed in full, Applicants respectfully request withdrawal of all outstanding rejections and the issuance of a Notice of Allowance forthwith. The Examiner is encouraged to address any questions regarding the foregoing to the undersigned attorney, who may be reached at (919) 854-1400. The Commissioner is hereby

authorized to charge Deposit Account No. 50-0220 for any additional extension and/or fee required or credit for any excess fee paid.

Respectfully submitted,

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